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Lack of periconceptional vitamins or supplements that contain folic acid and diabetes mellitus–associated birth defects

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Abstract

OBJECTIVE—The purpose of this study was to examine the risk of birth defects in relation to diabetes mellitus and the lack of use of periconceptional vitamins or supplements that contain folic acid.

STUDY DESIGN—The National Birth Defects Prevention Study (1997-2004) is a multicenter, population-based case-control study of birth defects (14,721 cases and 5437 control infants). Cases were categorized into 18 types of heart defects and 26 noncardiac birth defects. We estimated odds ratios for independent and joint effects of preexisting diabetes mellitus and a lack of periconceptional use of vitamins or supplements that contain folic acid.

RESULTS—The pattern of odds ratios suggested an increased risk of defects that are associated with diabetes mellitus in the absence vs the presence of the periconceptional use of vitamins or supplements that contain folic acid.

CONCLUSION—The lack of periconceptional use of vitamins or supplements that contain folic acid may be associated with an excess risk for birth defects due to diabetes mellitus.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Keywords

birth defect; diabetes mellitus; folic acid; supplement; vitamin

Offspring of mothers with preexisting diabetes mellitus (ie, type 1 or 2) have a 2- to 4-fold increased risk for a wide spectrum of birth defects.¹⁻³ Human studies have shown that hyperglycemia during organogenesis is associated with an increased risk for birth defects and that this risk correlates directly with maternal glucose levels.⁴⁻⁷ However, animal studies have suggested a complex pathogenetic process that also involves excess concentrations of other biochemical abnormalities that are associated with hyperglycemia (eg, elevated triglycerides, branched-chain amino acids, β -hydroxy-butyrate, somatomedin inhibitors, and reactive oxygen species) as potential cofactors in diabetic embryopathy.⁸⁻¹⁰

Multidisciplinary preconception care programs that are focused on glucose monitoring and control during the periconceptional period have been associated with a reduction in prevalence of birth defects among offspring of pregnancies that were complicated by preexisting diabetes mellitus.^{11,12} However, continuing occurrence of birth defects among offspring of pregnancies that are complicated by preexisting diabetes mellitus^{1,2,13} underscores ongoing challenges that face prevention efforts. One challenge is that approximately one-third of reproductive aged women with preexisting diabetes mellitus are undiagnosed.¹⁴ Furthermore, >60% of women with preexisting diabetes mellitus have unplanned pregnancies, lack access to preconception care, or might find it difficult to comply with prescribed glycemic control regimens.¹⁵⁻¹⁷

Holding some promise for prevention efforts are reports from animal studies that suggest that high doses of certain antioxidants (eg, vitamins C and E),^{18,19} fatty acids (eg, lipoic acid and arachidonic acid),^{20,21} and possibly folic acid^{22,23} can reduce the risk for birth defects among pregnancies that are complicated by diabetes mellitus. Human studies have demonstrated that maternal periconceptional use of folic acid or multivitamin supplements that contain folic acid reduces the risk for neural tube defects.^{24,25} However, evidence of similar risk reduction for other defects has been less consistent.^{26,27}

Because offspring of women with preexisting diabetes mellitus are at increased risk for neural tube defects, the American Diabetes Association supports the US Public Health Service recommendation that women who are capable of becoming pregnant consume 400 μ g of folic acid daily from all sources and further stipulates that, during periconceptional and prenatal periods, women with preexisting diabetes mellitus increase their folic acid intake to 600 μ g daily through supplements or fortified food sources.^{12,28} However, data on efficacy of periconceptional folic acid in-take regarding the risk of birth defects among women with preexisting diabetes mellitus are limited.²⁹

We used the National Birth Defects Prevention Study (NBDPS), which is a population-based, case-control study of birth defects, to examine the independent and joint effects of preexisting diabetes mellitus and the absence of periconceptional intake of vitamins or supplements that contain folic acid on the occurrence of birth defects.

Materials and Methods

Study population

The NBDPS is an ongoing study that is based on birth defects surveillance systems in the following states: Arkansas, California, Georgia/Centers for Disease Control and Prevention, Iowa, Massachusetts, New Jersey (through 2002), New York, North Carolina (beginning 2003), Texas, and Utah (beginning 2003).³⁰ Case infants who were selected for the study had at least 1 of >30 eligible birth defects and were liveborn, stillborn, or electively terminated. Case records were reviewed systematically by clinical geneticists to exclude case infants with recognized or strongly suspected single-gene conditions or chromosomal abnormalities. Control infants were liveborn infants without birth defects who were selected randomly either from birth certificates or hospital birth records. Mothers were interviewed in either English or Spanish by telephone 6 weeks to 24 months after the estimated date of delivery with the use of a computer-based questionnaire. Interviewers obtained information on maternal demographic characteristics, exposures (eg, nutritional, behavioral, or occupational), and medication use both before and during pregnancy. Interview participation rates were 70% among mothers of case infants and 67% among mothers of control infants. The NBDPS was approved by the institutional review boards of the Centers for Disease Control and Prevention and the participating study centers.

Clinical information on case infants was reviewed by a team of clinical geneticists and clinicians with expertise in pediatric cardiology.^{31,32} Case infants were classified as having an isolated birth defect if they had (a) 1 major birth defect only; (b) 1 major birth defect and 1 minor birth defects; (c) 1 major birth defects that affect 1 organ system only; or (d) 1 major birth defect with a well-described sequence of related defects and no major unrelated birth defects. Case infants were classified as having multiple birth defects if they had 2 major unrelated defects in different organ systems.³¹ For case infants with a congenital heart defect (CHD), an additional layer of classification was used to denote “simple” cases as anatomically discrete or having a well-recognized single malformation (eg, hypoplastic left heart syndrome or tetralogy of Fallot).³²

Definitions of exposures and covariates

All information was self-reported during the maternal telephone interviews. Mothers reported whether a physician had diagnosed them previously with preexisting diabetes mellitus or gestational diabetes mellitus. Based on such reports, we classified case and control infants into 1 of 4 mutually exclusive categories: (1) infant of a mother with preexisting diabetes mellitus, if the mother reported having been diagnosed with type 1 or type 2 diabetes mellitus before the estimated date of conception of the index infant; (2) infant of a mother with gestational diabetes mellitus, if the mother reported having been diagnosed with gestational diabetes mellitus during the index pregnancy; (3) infant of a nondiabetic mother, if the mother reported never having been diagnosed with any type of diabetes mellitus; and (4) unknown, if the response was missing or inconstant (maternal report of preexisting diabetes mellitus diagnosed during the index pregnancy). The current analyses covered only infants of mothers who had been classified into categories 1 and 3.

Mothers were asked about their use of a multivitamin, prenatal vitamin, or single-component vitamin, including information on the product brand used, start and stop dates (and/or duration of use), and frequency of use. If exact dates of use were unknown, mothers could report less specific information, such as a pregnancy month (eg, first month of pregnancy) or time of year (eg, beginning of the year), which was converted into dates to determine the timing of the use in relation to the pregnancy. NBDPS investigators determined whether the specific product that was reported contained folic acid.³³ Periconceptional users of vitamins or supplements that contain folic acid were identified as mothers who reported any use during the month before conception or during the first 3 months of pregnancy. Those who reported no use during the entire time period from 1 month before conception through the end of the first trimester were considered nonusers. Mothers with an unknown intake, those who began in-take after the end of the first trimester, or those who began (and ended) intake before the start of the month before conception were excluded from these analyses.

Several covariates were considered potential confounders. Self-reported prepregnancy height and weight were converted to metric units and maternal body mass index was calculated as weight in kilograms divided by height in square meters (kg/m^2). Four body mass index groups were formed: (1) underweight ($<18.5 \text{ kg}/\text{m}^2$), (2) normal weight ($18.5\text{-}24.9 \text{ kg}/\text{m}^2$), (3) overweight ($25.0\text{-}29.9 \text{ kg}/\text{m}^2$), and (4) obese ($\geq 30.0 \text{ kg}/\text{m}^2$).³⁴ Additional variables included maternal age (<20 , 20-24, 25-29, 30-34, and ≥ 35 years), maternal race or ethnicity (non-Hispanic white, non-Hispanic black or African American, Hispanic, and other race or ethnicity), timing of entry into prenatal care (≥ 10 weeks gestation vs later), annual household income ($\geq \$40,000$ vs less), and parity (first vs subsequent livebirth).

Exclusions

Case and control infants who were delivered during the period from October 1, 1997, through December 31, 2004, were eligible for this study. We restricted the analysis to case and control mothers with preexisting diabetes mellitus (type 1 or type 2) with a known date of diagnosis (month and year) before the index pregnancy and mothers with no diabetes mellitus of any type. Of the 16,419 case mothers and 5958 control mothers who participated in the NBDPS, 1313 case and 386 control mothers with gestational diabetes mellitus or with unknown or inconsistent diabetes mellitus status were excluded, as were 441 case and 147 control mothers who were neither definitive users nor nonusers of vitamins or supplements that contain folic acid during the period of 1 month before pregnancy through the third month of pregnancy. Because 56 case and 12 control mothers met both exclusion criteria, the final analyses comprised 14,721 case mothers and 5437 control mothers. Control infants who were included in the analyses of hypospadias were restricted to male infants only.

Statistical analysis

We conducted multiple logistic regressions using the covariates that were described previously to estimate relative risks with adjusted odds ratios and 95% confidence intervals. We evaluated the independent and joint effects of preexisting diabetes mellitus and the absence of the periconceptional intake of vitamins or supplements that contain folic acid by comparing the risk for birth defects among 4 mutually exclusive groupings of mothers: (1) mothers without diabetes mellitus with periconceptional intake of vitamins or supplements

that contain folic acid (reference group), (2) mothers without diabetes mellitus with no periconceptional intake of vitamins (the “independent” effect of no periconceptional intake), (3) mothers with preexisting diabetes mellitus with periconceptional intake of vitamins that contain folic acid (the “independent” effect of preexisting diabetes mellitus), and (4) mothers with preexisting diabetes mellitus with no periconceptional intake of vitamins (joint effect). To assess whether there was an interaction between diabetes mellitus and a lack of intake of vitamins that contain folic acid that departed from additivity of effects, we calculated the relative excess risk due to interaction (RERI) and its 95% confidence interval. The confidence intervals were calculated based on Taylor expansions of the variances and covariances from the multiple logistic regression models. A spreadsheet (Microsoft Excel, version 1997-2003; Microsoft Corporation, Redmond, WA) that was developed by Andersson et al³⁵ and available at www.epinet.se facilitated these calculations. RERI estimates greater than zero suggested superadditive effects, although estimates equal to zero suggested additive effects only.

We assessed the sensitivity of our results to certain exclusions and definitions by looking at changes in estimates associated with (1) the exclusion of multiple gestations and a first-degree family history of birth defects (2 strong, but uncommon, risk factors), (2) changes in the definition of periconceptional intake of vitamins or supplements that contain folic acid (ie, changes in the gestational months of periconceptional use), and (3) the restriction of the analyses to cases of isolated birth defects only. All analyses were conducted with SAS software (version 9.2; SAS Institute, Inc, Cary, NC).

Results

The prevalence of preexisting diabetes mellitus was 0.5% among control mothers and 2.4% among case mothers. Reported use of vitamins that contain folic acid in the periconceptional period (ie, in the month before conception or the first 3 months of pregnancy) was similar in both groups, approximately 87%. Fifty-seven case mothers (0.4%) and only 2 control mothers were in the hypothesized group at highest risk (those with preexisting diabetes mellitus and without periconceptional intake of vitamins that contain folic acid). Case and control mothers differed in this joint distribution. They also differed with respect to body mass index, education, parity, household income, and timing of entry into prenatal care (Table 1).

Tables 2 and 3 show the independent and joint effect estimates of the association between maternal preexisting diabetes mellitus and the lack of periconceptional intake of vitamins or supplements that contain folic acid and the occurrence of CHDs and noncardiac birth defects, respectively. RERI could be calculated for 9 of 13 specific types of CHDs. For 8 of these 9 specific types of CHDs (Table 2), there was a suggestion of superadditive effects (RERI estimate, >0); for any CHD, there was an increased point estimate for the effect of preexisting diabetes mellitus in the absence of the periconceptional intake of vitamins that contain folic acid compared with the effect of preexisting diabetes mellitus in the presence of vitamin intake that contains folic acid (eg, any CHD: No, No = 1.13; Yes, Yes = 5.51; Yes, No = 13.35). For 4 CHD subtypes, there were no case infants in the highest risk group; therefore, the RERI could not be calculated. Of the 8 specific CHD subtypes with RERI

estimates of >0 , 6 subtypes had estimates of >2.0 and a point estimate for the joint effect of preexisting diabetes mellitus in the absence of periconceptional intake of vitamins that contain folic acid approximately 2 times that of the effect of preexisting diabetes mellitus in the presence of periconceptional intake of vitamins. However, the RERI estimates were imprecise and did not reach statistical significance for any of the types of CHDs or CHD groups.

A similar pattern was seen for noncardiac birth defects (Table 3). Independent and joint effects could be calculated for 13 of 21 specific types of these birth defects, for 9 of which there were suggestive synergistic effects (RERI, >0). The analyses for 8 of these 13 types of birth defects yielded RERI estimates of >2.0 and an estimate of the odds of a case for the joint effect of preexisting diabetes mellitus with no periconceptional intake of vitamins that contain folic acid approximately 2 times that of the odds of a case for preexisting diabetes mellitus with periconceptional intake of vitamins that contain folic acid. A negative RERI was obtained for only 1 type of birth defect, anotia-microtia. Again, however, the RERI estimates were imprecise and not statistically significant.

Sensitivity analyses that restricted the study sample to singleton births (case infants, 94%; control infants, 97%) or to case infants without a first-degree family history of the birth defect of interest (94-100% of each case group) and control infants without a first-degree family history of any birth defect (98% of control infants) did not yield meaningfully different results. Similarly, the restriction of the analyses to isolated case infants (or infants with simple, isolated CHD) or the use of a more conservative definition of supplement use (1 month before to 1 month after the date of conception) did not change the results appreciably but increased the confidence intervals considerably and led to less distinction in effect estimates between the exposure groups (data not shown).

Comment

We found evidence for an association between preexisting diabetes mellitus and increased risk for birth defects despite the use of vitamins or supplements that contain folic acid. Our findings for specific birth defects were limited by small numbers of case mothers who were exposed jointly to preexisting diabetes mellitus and no periconceptional use of vitamins or supplements that contain folic acid. However, there was evidence to suggest that the offspring of mothers with preexisting diabetes mellitus and no periconceptional use of vitamins or supplements that contain folic acid experienced at least a nonstatistically significant 2-fold greater risk for birth defects when compared with the offspring of mothers with preexisting diabetes mellitus who reported the periconceptional use of vitamins or supplements that contain folic acid.

Strengths of this study included the large representative sample and standardized procedures for case definition and classification of birth defects. The control population was a representative sample of infants without defects from the delivery cohorts that gave rise to the infants with birth defects.^{30,36} Case infants were identified by population-based surveillance systems that used multiple sources for ascertainment. In addition, interview

participation rates were comparable for case and control mothers, and our findings changed little with adjustment for potential confounders.

Our classification of diabetes mellitus that was based on maternal reports of diagnosed diabetes mellitus was similar to that used in previous population-based, case-control studies of birth defects.^{1,37} Because self-reports of diabetes mellitus tend to have <100% sensitivity,^{38,39} the underreporting of diabetes mellitus by women with a previous diagnosis of diabetes mellitus probably resulted in a lower prevalence of preexisting diabetes mellitus in pregnancy among our study control women (0.5%) than that reported among pregnant women in the general population (0.75%), where the diagnosis of preexisting diabetes mellitus was based on hospital discharge data.⁴⁰ Because some women with diabetes mellitus might have been undiagnosed, it is possible that a fraction of the women who reported having no diabetes mellitus actually might have had undiagnosed type 2 diabetes mellitus, which would result in further exposure misclassification. Because there was no reason to believe that the resultant misclassification of diabetes mellitus status occurred differently for case and control mothers, the net effect of such misclassification probably was of an attenuation of associations of diabetes mellitus with birth defects.

The low prevalence of reported preexisting diabetes mellitus limited our ability to obtain reliable estimates for the joint effect of preexisting diabetes mellitus and the lack of use of vitamins or supplements that contain folic acid on the risk for birth defects. For approximately 33% of the specific types of birth defects (12/35 defects), we were not able to obtain an estimate of a joint effect because of a lack of case mothers in this exposure category. However, a consistent pattern of a greater odds ratio for the joint effect of preexisting diabetes mellitus and no periconceptional vitamin or supplement use other than for the independent effect of preexisting diabetes mellitus (in the presence of periconceptional vitamin or supplement use) for approximately 75% of the specific types of birth defects (17/23 defects) examined is noteworthy and warrants corroboration.

Our assessment of the independent and joint effects of diabetes mellitus and the lack of use of supplements that contain folic acid was based on the assumption that the level of glycemic control was similar across groups of women with diabetes mellitus, regardless of supplement use. However, it is likely that women with diabetes mellitus who used supplements also planned their pregnancies and therefore may have had better glycemic control before and early in pregnancy than women with diabetes mellitus who did not use supplements and who may not have planned their pregnancies. Because the timely institution of intensive glycemic control for pregnant women with insulin-dependent diabetes mellitus has been associated with the rates of birth defects that are similar to those observed among pregnant women who did not have diabetes mellitus,^{4,6,41} it is possible that the apparent synergistic effects of diabetes mellitus and the lack of supplement use may reflect underlying differences in pregnancy planning and diabetes mellitus control rather than an effect of a lack of supplement use per se. This possibility remains an important consideration, given that >50% of women with diabetes mellitus do not plan their pregnancies and that we did not have information on the level of glycemic control among case and control mothers.

The validity of self-reported supplement intake is likely to be high,^{42,43} particularly with regard to folic acid content, given the predominant intake of prenatal supplements that have relatively standard folic acid content. The extent of error in the reported dates of intake, however, is unknown. Our definition of supplement intake (ie, any use during the month before conception or during the first 3 months of pregnancy) was more inclusive than the ones that were used in other studies and may explain the higher prevalence of supplement use that was observed in our study. We chose a more inclusive definition of supplement use to provide more precise point estimates for the associations of interest, albeit at the risk of being biased towards the null.

Our finding of no consistent association between neural tube defects and maternal supplement use among the off-spring of women without preexisting diabetes mellitus differed from observations in studies that were conducted before the era of folic acid fortification (ie, 1998). Those studies were generally consistent regarding a protective effect of the periconceptional use of folic acid against neural tube defects and formed the basis for the US Public Health Service recommendation that women who were capable of becoming pregnant should consume 400 μg of folic acid each day.^{24,25,28} Our findings on neural tube defects and supplement use, however, were consistent with a report of recent decreases in the prevalence of low serum ($<3 \text{ ng/mL}$) and red blood cell ($<140 \text{ ng/mL}$) folate levels among women of childbearing age in the United States (20.6-0.6% and 37.6-5.5%, respectively, from 1988-1994 to 2003-2004).⁴⁴ Another possibility that could explain the lack of a protective effect of supplement use against neural tube defects is that some pregnancies that were affected by neural tube defects in the study birth cohort were terminated without being enrolled in the study.

Our finding that offspring of women with preexisting diabetes mellitus who reported no periconceptional use of vitamins or supplements that contain folic acid appeared to be at greater risk for birth defects than the offspring of women with preexisting diabetes mellitus who had reported use of vitamins or supplements that contain folic acid is consistent with that of a previous epidemiologic study.²⁹ This observation also is consistent with results from animal studies among pregnancies that were complicated by diabetes mellitus and showed that the administration of high doses of the antioxidant vitamins E and C,^{18,45} certain fatty acids,^{20,21,46} or folic acid can prevent diabetic embryopathy.^{22,23,47} In our study, we had adequate information to classify supplements that contain folic acid and those that contain vitamin E or C. However, we had no information on the concentration of micronutrients or on the dose that was taken. Furthermore, we found a high concordance between the intake of supplements that contain folic acid and supplements that contain vitamins E and C, which made it difficult to evaluate the independent and joint effects of intake of these different types of micronutrients. As in a previous study, we were not able to account for potential confounding by the level of glycemic control, which still remains to be another possible explanation for our findings.

The risk of birth defects among women with preexisting diabetes mellitus remains very high. Prevention of the excess of birth defects for children who are born to women with preexisting diabetes mellitus would make a marked improvement in the health of children. So far, we have made little progress in reaching this goal. The strongest evidence we have,

and we have only observational data, is that good glucose control before and early in pregnancy is associated with a lower risk of birth defects. Until there is better evidence, we should seek to improve glucose control of all women of reproductive age who have preexisting diabetes mellitus, especially among those who are planning a pregnancy. All women of reproductive age should be encouraged to consume enough folic acid. In countries such as Europe where there is no required folic acid fortification, all women of reproductive age should be encouraged to consume vitamin supplements that contain folic acid because it is known from randomized controlled trials that such consumption will prevent spina bifida and anencephaly. In countries such as the United States and Canada where there is fortification, there is uncertainty about what additional prevention may occur from consuming a multivitamin with folic acid. Our data are consistent with the idea (but it is far from established) that such consumption may decrease the risk of certain birth defects among the offspring of women with preexisting diabetes mellitus.

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TABLE 1

Characteristics of mothers of control and case infants: National Birth Defects Prevention Study, 1997-2004

Characteristic	Control infants (n = 5437)		Case infants (n = 14,721)		P value
	n	%	n	%	
Preexisting diabetes mellitus	29	0.5	346	2.4	< .0001
Periconceptual ^a intake of vitamins or supplements that contain folic acid	4764	87.6	12,791	86.9	.17
Joint distribution of preexisting diabetes mellitus and periconceptual ^a intake of vitamins or supplements that contain folic acid					< .0001
No diabetes mellitus, yes periconceptual intake	4737	87.1	12,502	84.9	
No diabetes mellitus, no periconceptual intake	671	12.3	1873	12.7	
Yes preexisting diabetes mellitus, yes periconceptual intake	27	0.5	289	2.0	
Yes preexisting diabetes mellitus, no periconceptual intake	2	0.0	57	0.4	
Body mass index, kg/m ²					.002
<18.5	306	5.6	849	5.8	
18.5–25.0	2993	55.0	7760	52.7	
25.0–30.0	1142	21.0	3152	21.4	
30.0	788	14.5	2420	16.4	
Missing	208	3.8	540	3.7	
Age, y					.71
<20	616	11.3	1730	11.8	
20–24	1249	23.0	3482	23.7	
25–29	1433	26.4	3744	25.4	
30–34	1398	25.7	3615	24.6	
35	741	13.6	2150	14.6	
Education					.002
<High school	890	16.4	2575	17.5	
High school	1329	24.4	3820	25.9	
>High school	3166	58.2	8202	55.7	
Missing	124	2.3	52	0.4	
Race and ethnicity					.65
Non-Hispanic white	3288	60.5	8952	60.8	
Non-Hispanic black or African American	623	11.5	1517	10.3	
Hispanic	1180	21.7	3290	22.3	
Other	329	6.1	920	6.2	
Missing	17	0.3	42	0.3	
Parity					< .0001
First livebirth	2235	41.1	6567	44.6	
Second or subsequent livebirth	3201	58.9	8148	55.3	
Missing	1	0	6	0	
Multiple gestation pregnancy	155	2.9	911	6.2	< .0001
Household income \$40,000/y ^b	2122	39.0	5596	38.0	.009

Characteristic	Control infants (n = 5437)		Case infants (n = 14,721)		P value
	n	%	n	%	
Entry into prenatal care at or before 10 weeks gestation ^c	3614	66.5	9975	67.8	.04

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^a Any intake in the month before conception or during the first 3 months of pregnancy

^b Household income was missing for 3% of control infants and 6.5% of case infants

^c Prenatal care information was missing for 0.3% of control infants and 1% of case infants.

TABLE 2

Independent and joint effect estimates for selected congenital heart defects: National Birth Defects Prevention Study, 1997-2004

Congenital heart defect	Maternal diabetes mellitus ^a	Use of vitamins ^b	Case infants: control infants	Odds ratio (95% CI) ^c	Relative excess risk due to interaction (95% CI)
Any congenital heart defect	No	Yes	5206:4737	Reference	7.71 (−11.55 to 26.97)
	No	No	773:671	1.13 (0.99–1.30)	
	Yes	Yes	180:27	5.51 (3.60–8.42)	
	Yes	No	35:2	13.35 (3.18–55.96)	
Heterotaxia	No	Yes	128:4737	Reference	Not calculated
	No	No	34:671	1.25 (0.76–2.05)	
	Yes	Yes	9:27	11.94 (5.06–28.20)	
	Yes	No	0:2	Not calculated	
Any conotruncal defect	No	Yes	1034:4737	Reference	5.73 (−14.71 to 26.18)
	No	No	140:671	1.09 (0.86–1.38)	
	Yes	Yes	41:27	6.41 (3.82–10.77)	
	Yes	No	7:2	12.23 (2.3–63.93)	
Truncus arteriosus	No	Yes	43:4737	Reference	28.89 (−114.00 to 171.78)
	No	No	6:671	1.22 (0.40–3.69)	
	Yes	Yes	6:27	24.93 (8.99–69.13)	
	Yes	No	2:2	54.04 (3.85–759.21)	
Tetralogy of Fallot	No	Yes	460:4737	Reference	11.91 (−18.19 to 42.02)
	No	No	59:671	0.99 (0.70–1.41)	
	Yes	Yes	16:27	4.57 (2.28–9.16)	
	Yes	No	3:2	16.48 (2.67–101.80)	
D-transposition of the great arteries	No	Yes	320:4737	Reference	0.81 (−18.02 to 19.65)
	No	No	50:671	1.51 (1.05–2.17)	
	Yes	Yes	9:27	6.16 (2.80–13.56)	
	Yes	No	2:2	7.49 (0.65–85.72)	
Atrioventricular septal defect	No	Yes	122:4737	Reference	42.49 (−71.02 to 156.00)
	No	No	18:671	1.26 (0.69–2.29)	
	Yes	Yes	8:27	12.24 (5.17–28.93)	
	Yes	No	2:2	54.98 (7.00–432.12)	
Total anomalous pulmonary venous return	No	Yes	122:4737	Reference	Not calculated
	No	No	16:671	0.94 (0.50–1.76)	
	Yes	Yes	3:27	4.82 (1.40–16.64)	
	Yes	No	0:2	Not calculated	

Congenital heart defect	Maternal diabetes mellitus ^a	Use of vitamins ^b	Case infants: control infants	Odds ratio (95% CI) ^c	Relative excess risk due to interaction (95% CI)
Any left ventricular outflow tract obstruction defect	No	Yes	840:4737	Reference	1.59 (−9.34 to 12.51)
	No	No	84:671	0.79 (0.59–1.06)	
	Yes	Yes	19:27	4.01 (2.15–7.48)	
	Yes	No	2:2	5.39 (0.75–38.93)	
Hypoplastic left heart syndrome	No	Yes	246:4737	Reference	Not calculated
	No	No	21:671	0.58 (0.32–1.05)	
	Yes	Yes	6:27	3.42 (1.27–9.22)	
	Yes	No	0:2	Not calculated	
Coarctation of the aorta	No	Yes	434:4737	Reference	4.42 (−13.18 to 22.03)
	No	No	52:671	0.96 (0.67–1.38)	
	Yes	Yes	10:27	4.32 (2.02–9.24)	
	Yes	No	2:2	8.70 (1.19–63.88)	
Aortic stenosis	No	Yes	191:4737	Reference	Not calculated
	No	No	13:671	0.58 (0.30–1.13)	
	Yes	Yes	5:27	5.35 (1.95–14.68)	
	Yes	No	0:2	Not calculated	
Any right ventricular outflow tract obstruction defect	No	Yes	726:4737	Reference	4.58 (−9.47 to 18.63)
	No	No	112:671	1.28 (0.99–1.65)	
	Yes	Yes	15:27	2.83 (1.42–5.62)	
	Yes	No	3:2	7.69 (1.25–47.18)	
Pulmonary atresia	No	Yes	107:4737	Reference	12.38 (−26.41 to 51.61)
	No	No	14:671	1.06 (0.56–2.00)	
	Yes	Yes	2:27	3.01 (0.68–13.25)	
	Yes	No	1:2	15.45 (1.26–189.12)	
Pulmonary valve stenosis ^d	No	Yes	569:4390	Reference	2.43 (−9.61 to 14.47)
	No	No	86:599	1.29 (0.97–1.72)	
	Yes	Yes	12:24	3.22 (1.53–6.78)	
	Yes	No	2:2	5.94 (0.81–43.52)	
Ventricular septal defect: perimembranous	No	Yes	928:4737	Reference	5.35 (−12.16 to 22.86)
	No	No	152:671	1.25 (0.99–1.57)	
	Yes	Yes	28:27	4.43 (2.51–7.82)	
	Yes	No	5:2	10.03 (1.77–56.66)	
Atrial septal defect: secundum or not otherwise specified	No	Yes	1274:4737	Reference	9.45 (−15.70 to 34.59)
	No	No	227:671	1.25 (1.03–1.53)	
	Yes	Yes	56:27	6.76 (4.16–10.98)	
	Yes	No	11:2	16.46 (3.61–75.07)	

CI, confidence interval.

Correa. Lack of folic acid supplements and diabetes mellitus–associated birth defects. *Am J Obstet Gynecol* 2012.

^aFor maternal diabetes mellitus: Yes = preexisting diabetes mellitus; No = no diabetes mellitus of any type

^bFor use of vitamins: Yes = any use from the period of 1 month before pregnancy through the third month of pregnancy of a vitamin or supplement that contains folic acid; No = no use during the month before conception and the first 3 months of pregnancy of a vitamin or supplement that contains folic acid

^cAdjusted for maternal age, race, and ethnicity, entry into prenatal care, prepregnancy body mass index, parity, and household income

^dNote the different number of control infants for pulmonary valve stenosis because of limited ascertainment in California.

TABLE 3

Independent and joint effect estimates for selected noncardiac birth defects: National Birth Defects Prevention Study, 1997–2004

Birth defect	Maternal diabetes mellitus ^a	Use of vitamins ^b	Case infants: control infants	Odds ratio (95% CI) ^c	Relative excess risk due to interaction (95% CI)
Any birth defect	No	Yes	12502:4737	Reference	5.92 (–7.96 to 19.79)
	No	No	1873:671	1.12 (1.00–1.26)	
	Yes	Yes	289:27	3.27 (2.46–5.63)	
	Yes	No	57:2	9.77 (2.38–40.12)	
Any neural tube defect	No	Yes	787:4737	Reference	6.65 (–7.83 to 21.14)
	No	No	138:671	1.08 (0.84–1.38)	
	Yes	Yes	10:27	1.66 (0.73–3.74)	
	Yes	No	4:2	8.39 (1.50–46.89)	
Anencephaly	No	Yes	233:4737	Reference	29.72 (–28.54 to 87.99)
	No	No	32:671	1.03 (0.65–1.63)	
	Yes	Yes	2:27	1.80 (0.42–7.81)	
	Yes	No	3:2	31.56 (4.98–199.94)	
Spina bifida	No	Yes	470:4737	Reference	0.69 (–5.25 to 6.64)
	No	No	84:671	1.02 (0.75–1.38)	
	Yes	Yes	5:27	1.66 (0.62–4.42)	
	Yes	No	1:2	2.37 (0.21–26.68)	
Encephalocele	No	Yes	84:4737	Reference	Not calculated
	No	No	22:671	1.60 (0.88–2.92)	
	Yes	Yes	3:27	1.84 (0.24–14.13)	
	Yes	No	0:2	Not calculated	
Hydrocephaly	No	Yes	204:4737	Reference	20.03 (–26.68 to 66.74)
	No	No	34:671	0.97 (0.60–1.55)	
	Yes	Yes	8:27	5.63 (2.36–13.41)	
	Yes	No	3:2	25.63 (4.16–158.02)	
Holoprosencephaly	No	Yes	48:4737	Reference	Not calculated
	No	No	13:671	1.52 (0.69–3.39)	
	Yes	Yes	2:27	9.06 (1.97–41.77)	
	Yes	No	0:2	Not calculated	
Anotia-Microtia	No	Yes	263:4737	Reference	–1.51 (–16.30 to 13.28)
	No	No	53:671	1.01 (0.69–1.48)	
	Yes	Yes	13:27	7.07 (3.27–15.28)	
	Yes	No	1:2	5.57 (0.46–66.97)	

Birth defect	Maternal diabetes mellitus ^a	Use of vitamins ^b	Case infants: control infants	Odds ratio (95% CI) ^c	Relative excess risk due to interaction (95% CI)
Choanal atresia	No	Yes	70:4737	Reference	Not calculated
	No	No	9:671	1.27 (0.55–2.95)	
	Yes	Yes	0:27	Not calculated	
	Yes	No	1:2	45.96 (3.54–597.50)	
Any oral cleft ^d	No	Yes	1835:4613	Reference	11.36 (–9.78 to 32.51)
	No	No	315:665	1.30 (1.09–1.55)	
	Yes	Yes	23:27	2.17 (1.20–3.93)	
	Yes	No	11:2	13.84 (3.01–63.68)	
Cleft palate ^d	No	Yes	642:4613	Reference	0.50 (–8.14 to 8.24)
	No	No	103:665	1.54 (1.18–2.01)	
	Yes	Yes	10:27	2.68 (1.26–5.68)	
	Yes	No	1:2	3.27 (0.29–37.13)	
Cleft lip with or without cleft palate ^d	No	Yes	1193:4613	Reference	17.30 (–12.59 to 47.19)
	No	No	212:665	1.20 (0.98–1.47)	
	Yes	Yes	13:27	1.83 (0.88–3.77)	
	Yes	No	10:2	19.33 (4.12–90.69)	
Esophageal atresia	No	Yes	311:4737	Reference	Not calculated
	No	No	38:671	1.03 (0.66–1.59)	
	Yes	Yes	6:27	3.25 (1.28–8.24)	
	Yes	No	0:2	Not calculated	
Ileal, jejunal, and multiple small intestinal atresias	No	Yes	182:4737	Reference	Not calculated
	No	No	34:671	1.32 (0.85–2.04)	
	Yes	Yes	0:27	Not calculated	
	Yes	No	0:2	Not calculated	
Anorectal atresia	No	Yes	422:4737	Reference	23.87 (–23.81 to 71.54)
	No	No	72:671	1.42 (1.03–1.95)	
	Yes	Yes	12:27	4.41 (2.08–9.38)	
	Yes	No	5:2	28.70 (5.46–150.97)	
Biliary atresia	No	Yes	73:4737	Reference	45.05 (–75.08 to 165.19)
	No	No	11:671	1.13 (0.55–2.33)	
	Yes	Yes	1:27	2.56 (0.33–19.53)	
	Yes	No	1:2	47.74 (3.85–592.05)	
Hypospadias ^d	No	Yes	966:2374	Reference	1.51 (–9.19 to 12.22)
	No	No	76:338	0.84 (0.60–1.15)	
	Yes	Yes	17:16	2.44 (1.14–5.20)	
	Yes	No	1:1	3.78 (0.23–61.46)	

Birth defect	Maternal diabetes mellitus ^a	Use of vitamins ^b	Case infants: control infants	Odds ratio (95% CI) ^c	Relative excess risk due to interaction (95% CI)
Bilateral renal agenesis/hypoplasia	No	Yes	67:4737	Reference	Not calculated
	No	No	17:671	2.38 (1.25–4.51)	
	Yes	Yes	4:27	12.24 (3.94–38.07)	
	Yes	No	1:2	Not calculated	
Any limb deficiency	No	Yes	500:4737	Reference	9.86 (–17.09 to 36.81)
	No	No	76:671	1.00 (0.73–1.37)	
	Yes	Yes	15:27	4.87 (2.44–9.72)	
	Yes	No	3:2	14.73 (2.39–90.85)	
Longitudinal limb deficiency	No	Yes	188:4737	Reference	18.48 (–31.43 to 68.40)
	No	No	25:671	0.94 (0.57–1.56)	
	Yes	Yes	7:27	6.37 (2.52–16.09)	
	Yes	No	2:2	24.79 (3.34–184.23)	
Transverse deficiency limb	No	Yes	289:4737	Reference	Not calculated
	No	No	48:671	1.04 (0.69–1.55)	
	Yes	Yes	4:27	2.43 (0.83–7.15)	
	Yes	No	0:2	Not calculated	
Craniosynostosis	No	Yes	551:4737	Reference	Not calculated
	No	No	52:671	0.98 (0.70–1.37)	
	Yes	Yes	5:27	1.57 (0.59–4.21)	
	Yes	No	0:2	Not calculated	
Diaphragmatic hernia	No	Yes	355:4737	Reference	4.34 (–10.83 to 19.50)
	No	No	45:671	0.86 (0.57–1.29)	
	Yes	Yes	5:27	2.00 (0.69–5.86)	
	Yes	No	1:2	6.20 (0.55–70.06)	
Omphalocele	No	Yes	194:4737	Reference	Not calculated
	No	No	26:671	1.09 (0.66–1.79)	
	Yes	Yes	4:27	2.77 (0.93–8.28)	
	Yes	No	0:2	Not calculated	
Gastroschisis	No	Yes	496:4737	Reference	Not calculated
	No	No	99:671	0.93 (0.69–1.25)	
	Yes	Yes	1:27	0.41 (0.05–3.49)	
	Yes	No	0:2	Not calculated	
Sacral agenesis	No	Yes	23:4737	Reference	98.41 (–314.14 to 510.96)
	No	No	3:671	1.56 (0.41–5.96)	
	Yes	Yes	9:27	82.35 (26.22–258.65)	
	Yes	No	2:2	181.32 (18.16–1810.96)	

CI, confidence interval.

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^aFor maternal diabetes mellitus: Yes = preexisting diabetes mellitus; No = no diabetes mellitus of any type

^bFor use of vitamins: Yes = any use from the period of 1 month before pregnancy through the third month of pregnancy of a vitamin or supplement that contains folic acid; No = no use during the month before conception and the first 3 months of pregnancy of a vitamin or supplement that contains folic acid

^cAdjusted for maternal age, race, and ethnicity, entry into prenatal care, prepregnancy body mass index, parity, and household income

^dNote different number of control infants for oral clefts because of limited ascertainment in Utah and different number of control infants for hypospadias because of restriction to male infants.